**Annals of Clinical and Analytical Medicine**
*Original Research*

# The frequency of ESBL producing bacterial infections and related antimicrobial susceptibility in ICU patients: A five-year longitudinal study



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**Abstract**

Aim: This study aimed to evaluate the incidence of nosocomial infections caused by extended-spectrum β-lactamase (ESBL) producing bacteria and related antimicrobial susceptibility in critically ill patients over a 5-year period.

Material and Methods: The retrospective study was carried out in critically ill patients infected with ESBL-producing pathogens during intensive care unit (ICU) stay. Participants' medical data between 2014 and 2018 were included. ESBL-positive isolates from clinical specimens were evaluated by species and antibiotic susceptibility.

Results: Ninety of 2456 critically ill patients had ESBL-positive bacterial infections. The mean age of the study sample was 58.7 ±19.1 years and 53.3% were males. ESBL-producing E. coli was noted in 60 (66.7%) patients, K. pneumoniae in 27 (30.0%) patients and K. oxytoca in 3 (3.3%) patients. Colistin (100%), meropenem (94.9%), imipenem (94.0%), and amikacin (90.0%) were active against ≥90% of ESBL-producing pathogens, while ertapenem (89.4%), fosfomycin (87.5%), tigecycline (80.0%) were active against ≥80% of pathogens in ICU. Susceptibility of ESBL producers was remarkably low against levofloxacin (30.8%) and ciprofloxacin (36.7%). The mortality rate of the sample was 25.5%.

Discussion: Our findings revealed that ESBL-producing E. coli was highly responsible for ESBL-positive bacterial infections in ICU. The continued efficacy of colistin, carbapenems and amikacin against ESBL-producing E. coli and K. pneumoniae was exhibited.

**Keywords**

Intensive Care Unit, ESBL-Producing Bacteria, Nosocomial Infection, Antibiotic Resistance-Susceptibility

DOI: 10.4328/ACAM.21589 Received: 2023-01-14 Accepted: 2023-02-14 Published Online: 2023-02-24 Printed: 2023-03-25 Ann Clin Anal Med 2023;14(Suppl 1):S26-30
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This study was approved by the Clinical Research Ethics Committee of Erciyes University (Date: 2019-09-11, No: 2019/603)

## Introduction

The extended-spectrum beta-lactamase (ESBL) producing bacteria, the strains of Enterobacteriaceae in particular, show resistance to several classes of antibiotics, limiting the antibiotic therapy choices in patients with nosocomial urinary tract infections (UTIs) and intraabdominal infections [1-4]. Hence, the critical rise in the worldwide prevalence of ESBL (+) Enterobacteriaceae is considered a great challenge in clinical practice given the associated risk of treatment failure, higher morbidity, longer hospital stay and adverse patient outcomes [5,6].

Intensive care unit (ICU) patients are particularly prone to nosocomial infections due to vulnerability related to underlying critical illness, frequent use of invasive procedures and exposure to antibiotics, in addition to limited treatment options due to multidrug-resistant (MDR) ESBL producers preventing provision of adequate treatment [2,4,7-9].

Given the variability in the prevalence of ESBL-producing strains and antimicrobial resistance rates in different geographic regions and over time, local surveillance studies are required to guide empiric treatment in accordance with the bacterial spectrum of pathogens and the extent of antimicrobial resistance [6,9].

This hospital-based descriptive study aimed to evaluate the frequency of ESBL-producing bacterial infections and related antimicrobial susceptibility in Anesthesiology and Medical ICU patients during a five-year period.

## Material and Methods

### *Study population*

Between 2014 and 2018, 2456 patients aged >18 years with nosocomial bacterial infection were screened. Critically ill patients infected with ESBL-producing bacteria during ICU stay were included in this hospital-based descriptive study conducted at ICUs of a tertiary care hospital during the study period.

The current study was approved by the local ethics committee. It was conducted in accordance with the Declaration of Helsinki.

### *Assessments*

Data on participants' demographics (age, gender), APACHE II score, comorbidities, risk factors of nosocomial infection due to ESBL-producing bacteria and clinical outcomes (need for mechanical ventilation (MV), ICU mortality) were recorded. ESBL-positive isolates from clinical specimens were assessed by species and susceptibility to antibiotics.

### *Definition of isolates and susceptibility testing*

Identification of isolated bacteria was performed via conventional methods using VITEK® 2 Compact (bioMérieux, Marcyl'Etoile, France) system. Susceptibility testing was performed with the disc diffusion method in accordance with the European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendations. ESBL production of isolates was determined by double disc synergy method.

### *Statistical analysis*

Descriptive statistics were used. Continuous data were presented as "mean ± standard deviation or median (minimum-maximum) according to the normal distribution with the Shapiro-Wilk test. Categorical data were presented as numbers (percentage (%)).

### *Ethical Approval*

Ethics Committee approval for the study was obtained.

## Results

### *Demographic and clinical data of the study sample*

A total of 90 critically ill adult patients infected with ESBL-producing bacteria during ICU stay were included (Figure 1).

The mean patient age was 58.7 (SD: 19.1, range, 18 to 96) years, and 53.3% of patients were males. The mean APACHE II score of the participants was 16.2±7.1 (Table 1).

Pulmonary disease (14.4%) and diabetes (13.3%), and hypertension (11.1%) were the most common comorbidities. Enteral nutrition (38.9%), transfusion (33.3%), and antibiotic use (25.5%) were the most commonly noted risk factors for developing nosocomial infection due to ESBL-producing bacteria. 55.6% of the participants needed MV treatment during the study period. ICU mortality was 25.5%, as shown in Table 1.

**Table 1.** Demographic and clinical characteristics of patients infected with ESBL producers.

| Patient demographics (n=90) | | |
|---|---|---|
| Age (year) | Mean ±SD | 58.7±19.1 |
| | Median (min-max) | 61.0 (18-96) |
| Male gender, n (%) | | 48 (53.3) |
| APACHE score, mean ±SD | | 16.2±7.1 |
| Comorbidity, n (%) | | |
| Pulmonary disease | | 13 (14.4) |
| Diabetes | | 12 (13.3) |
| Hypertension | | 10 (11.1) |
| Malignancy | | 9 (10.0) |
| Heart failure | | 5 (5.5) |
| Kidney disease | | 4 (4.4) |
| Neurological disease | | 2 (2.2) |
| Risk factors for nosocomial infection due to ESBL-producing bacteria, n (%) | | |
| Enteral nutrition | | 35 (38.9) |
| Transfusion | | 30 (33.3) |
| Antibiotic use | | 23 (25.5) |
| Total parenteral nutrition | | 22 (24.4) |
| Trauma | | 7 (7.8) |
| Obesity | | 6 (6.7) |
| Burn | | 1 (1.1) |
| Need for MV support, n (%) | | 50 (55.6) |
| ICU mortality, n (%) | | 23 (25.5) |

APACHE II score: Acute Physiology and Chronic Health Evaluation, ICU: Intensive care unit, MV: Mechanical ventilation.

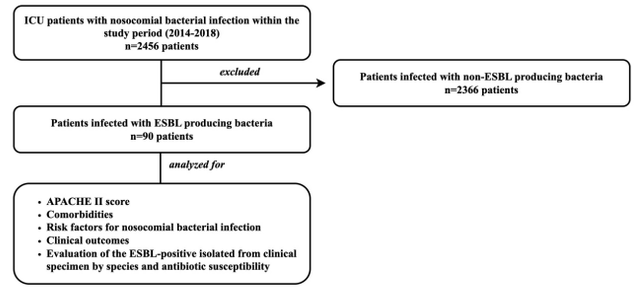


**Figure 1.** Study flowchart

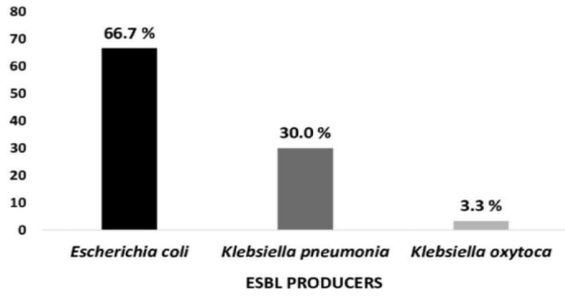


**Figure 2.** ESBL-positive isolates from clinical specimens by species.

**Table 2.** ESBL-positive isolates from clinical specimens by antibiotic susceptibility.

| | Antibiotic susceptibility, n (%) | | |
|---|---|---|---|
| | n | Sensitive | Resistant |
| Ciprofloxacin | 90 | 33 (36.7) | 57 (63.3) |
| Amikacin | 90 | 81 (90.0) | 1 (10.0) |
| Imipenem | 67 | 63 (94.0) | 4 (6.0) |
| Ertapenem | 66 | 59 (89.4) | 7 (10.6) |
| Meropenem | 59 | 56 (94.9) | 3 (5.1) |
| Gentamycin | 28 | 16 (57.1) | 1 (42.9) |
| Sulfamethoxazole-trimethoprim | 24 | 9 (37.5) | 15 (62.5) |
| Levofloxacin | 13 | 4 (30.8) | 9 (69.2) |
| Netilmicin | 9 | 7 (77.8) | 2 (22.2) |
| Fosfomycin | 8 | 7 (87.5) | 1 (12.5) |
| Nitrofurantoin | 7 | 5 (71.4) | 2 (28.6) |
| Colistin | 6 | 6 (100) | 0 |
| Tigecycline | 5 | 4 (80.0) | 1 (20.0) |

***ESBL-positive isolates from clinical specimens by species***

Overall, ESBL producers isolated from clinical specimens included ESBL-producing E.coli in 60 (66.7%) patients, K. pneumoniae in 27 (30.0%) patients and K. oxytoca in 3 (3.3%) patients (Figure 2).

***ESBL-positive isolates from clinical specimens by antibiotic susceptibility***

Of the drugs studied, colistin (100%), meropenem (94.9%), imipenem (94.0%), and amikacin (90.0%) were active against ≥90% of nosocomial infections due to ESBL-producing bacteria. Only ertapenem (89.4%), fosfomycin (87.5%), tigecycline (80.0%) were active against ≥80% of ESBL-producing bacteria (Table 2).

Susceptibility of ESBL-producing pathogens was remarkably low against levofloxacin (30.8%), ciprofloxacin (36.7%), and Sulfamethoxazole-trimethoprim (37.5%). The ESBL (+) isolates from clinical specimens by antibiotic susceptibility of study sample are shown in Table 2 in detail.

## Discussion

This hospital-based descriptive study revealed that the frequency of ESBL-positive bacterial infections in a tertiary care ICUs was 3.7% over a 5-year period. The ESBL-producing E. coli (66.7%) and K. pneumoniae (33.3%) were responsible causative pathogens, and ICU mortality rate was 25.5% with provision of enteral nutrition (38.9%) and blood transfusion (33.3%) being the main risk factors. Antimicrobial sensitivity testing revealed the continued efficacy of colistin, carbapenems, and amikacin against ESBL producing E. coli and K. pneumoniae along with resistance to fluoroquinolones and sulfamethoxazole-trimethoprim.

Data from worldwide SMART studies revealed a sustained increase in ESBL producing Enterobacteriaceae strains over time and indicated ESBL production rates for E. coli to range from 1.2%-64.9% and K. pneumoniae to range from 9.5%-46.8% [6,10,11]. High ESBL rates in Turkey have been consistently reported in multinational European studies such as 2004-2010 Tigecycline Evaluation and Surveillance Trial (30.9%) and the Regional Resistance Surveillance study for 2011 (>40.0%) [12,13]. Also, according to data from the HITIT study on analysis of 1196 gram-negative nosocomial isolates in Turkish hospitals in 2004-2005, among the blood isolates, E. coli (31.7% (33.3% in ICUs)) and K. pneumoniae (33.3%) were reported to produce ESBLs [9].

Our findings indicate ESBL-positive E. coli or K. pneumoniae as key pathogens for ICU-related infections during study period. In a past study conducted with 140 anesthesiology ICU patients in 2013 in Turkey, 41 (29.3%) of the patients were reported to be colonized with ESBL (+) E. coli (n=39) or K. pneumoniae (n=2) similar to our study. The ESBL (+) E. coli or K. pneumoniae colonization was determined as an independent risk factor for nosocomial infection development [2]. Notably, SMART 2011-2012 Turkey data revealed that the rate for ESBL (+) E. coli was lower (29.2 versus 52.5%) but the rate of ESBL-positive K. pneumoniae was higher (53.8 versus 39.6%) in the ICU setting than non-ICU setting for intraabdominal infections [6]. The authors also indicated the rates for both ESBL-positive E. coli (49.0%) and K. pneumoniae (44.0%) strains to be higher in Turkey [6] compared to global (2005-2007 and 2009-2010) and European (2002-2011) SMART rates [14,15] and to be compatible with some regions with especially high ESBL rates (e.g., Asia, Latin America, and the Middle East) [11, 16].

In the current study, of the drugs studied, colistin, meropenem, imipenem, and amikacin were sensitive to ≥90% of ESBL producing pathogens, while ertapenem, fosfomycin, tigecycline were active against ≥80% of pathogens in ICU. The susceptibility of ESBL producers was remarkably low against levofloxacin (30.8%), ciprofloxacin (36.7%), and Sulfamethoxazole-trimethoprim (37.5%). Likewise, SMART studies have shown that carbapenems and amikacin are highly susceptible to ESBL producing E. coli strains and K. pneumoniae strains along with resistance of Enterobacteriaceae against the cephalosporins, fluoroquinolones. The continued efficacy of carbapenems and amikacin against a wide range of Enterobacteriaceae was emphasized. [6,14,16-18].

In addition, previous studies from Turkey also indicated low susceptibility to cephalosporins due to increased ESBL (+) rates among E.coli and K. pneumoniae to limit empirical therapeutic options for the UTI treatment of hospital acquired in Turkey [6,19], while the increase in fosfomycin usage, particularly

for hospital acquired UTIs has also been noted due to low resistance rates against fosfomycin (~1.6%), rendering it a suitable alternative for empirical treatment in daily practice [19,20].

In a past study from Turkey in 2011, ESBL production was identified in 37(39 %) of 95 E. coli and K. pneumoniae strains, particularly in strains isolated from ICUs (65%) versus clinics (32%), while imipenem, meropenem and ertapenem were reported to be effective in all strains along with higher rates of resistance to antibiotics in ESBL positive versus negative E. coli strains [21]. In a 2010-2011 study from Turkey assessing 76 nosocomial ESBL-producing E. coli strains, most of ESBL-producing E. coli strains were reported to be isolated from samples of ICU patients (35%) followed by internal medicine ward (16%) and general surgery unit (13%). All 76 strains were reported to be sensitive to carbapenems and amikacin [22].

In a past study with 4,680 isolates from critically ill patients and 16,263 isolates from non-critically ill patients collected from 70 United States hospitals between 2018 and 2020, the authors reported the association of ICU versus non-ICU isolates with lower antimicrobial susceptibility and higher rate of ESBL, CRE, MDR, and XDR phenotypes [7]. The authors also noted that the most active agents against Enterobacteriaceae were ceftazidime-avibactam and meropenem-vaborbactam. Strong activity against ESBL producers, carbapenem-resistant Enterobacteriaceae, MDR, and XDR isolates was maintained [7].

A recent prospective study in India with 887 blood culture specimens of patients admitted to ICU with suspected sepsis reported that out of 202 (22.78%) blood culture specimens that yielded microbial growth, gram-negative bacteria (E. coli most commonly) accounted for 45.2% cases, while isolates of gram-negative were susceptible to colistin and tigecycline. 77.3% of isolates were ESBL producers [23]. Colistin and tigecycline sensitivity was evident in 66.7% and 71.4% of ESBL positive isolates in the current study.

Accordingly, it was found that particularly ESBL-producing E. coli and K. pneumoniae were responsible for nosocomial infections in most blood culture isolates from critically ill patients in ICU. Our findings support the consideration of multi-drug resistance as a significant problem associated with increase in hospital costs, duration of ICU stay and mortality [23]. In addition, antimicrobial sensitivity findings are also in consistent with past studies indicating the continued efficacy of carbapenems, amikacin and fosfomycin against ESBL-producing E. coli and K. pneumoniae along with resistance to fluoroquinolones and sulfamethoxazole-trimethoprim [6,7,14,16-18,24]. Indeed, given the likelihood of emergence of resistance particularly in Enterobacteriaceae to compromise the future utility of carbapenems, carbapenem-sparing alternative antibiotics are considered to be of highly importance for treatment strategies. Thus, the administration of carbapenems is suggested for patients who had severe and high inoculum-high risk infections with the use of various carbapenem-sparing antibiotics for milder infections, particularly for UTIs [25].

The retrospective and single center design seems to be the major limitation of our study. It cannot generalize our data to overall critically ill patients.

## *Conclusion*

Our findings revealed that ESBL-producing E. coli were highly responsible for ESBL-positive bacterial infections in ICUs. Colistin, carbapenems, amikacin and fosfomycin have been shown to be consistently effective against ESBL-producing E. coli and K. pneumoniae. The resistance to fluoroquinolones and sulfamethoxazole-trimethoprim showed the risk of increase in ESBL-producing bacterial infections in terms of limited effective treatment options over time in critically ill patients.

***Scientific Responsibility Statement***

*The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.*

***Animal and human rights statement***

*All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.*

***Funding:*** *None*

***Conflict of interest***

*None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.*

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***How to cite this article:***
***Sevda Onuk, Aliye Esmaoğlu Çoruh, Ayşegül Ulu Kılıç, Esma Eren, Kürşat Gündoğan.*** *The frequency of ESBL producing bacterial infections and related antimicrobial susceptibility in ICU patients: A five-year longitudinal study. Ann Clin Anal Med 2023;14(Suppl 1):S26-30*

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